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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,847	BULLEID, NEIL J.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-47* is/are pending in the application.

4a) Of the above claim(s) *45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Effective November 6, 2006, the location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Kevin K. Hill, Art Unit 1633.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on October 26, 2006 is acknowledged.

Applicant has elected the invention of Group I, Claims 29-44, drawn to a method of producing pro-collagen comprising expressing a nucleic acid in an isolated cell. Claims 45-47 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

2. Election of Applicant's invention(s) was made with traverse.

Applicant argues that the previous Examiner examined all of the claimed subject matter, that a determination was made that the claims do not define patentably distinct inventions, and that the previous Examiner suffered no undue search burden.

Applicants' arguments have been fully considered by the instant Examiner, but are not found persuasive. The instant Examiner notes that the previous Examiner explained in the Requirement for Restriction that the claimed subject matter did define patentably distinct inventions (pgs 2-3) and explained the nature of the search burden (pg 3).

MPEP §803 states that "If the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits, even though they include claims to independent or distinct inventions."

In the instant case a serious burden exists since each limitation, directed to a transgenic plant or non-human animal, requires a separate, divergent, and non co-extensive search and examination of the patent and non-patent literature. For instance, a search and consideration of the prior art as it relates to transgenic plants would not be adequate to uncover prior art related to transgenic cattle.

Further, a search and examination of all the claims directed to the recited embodiments involves different considerations of novelty, obviousness, written description, and enablement for each claim. In view of these requirements, it is the Examiner's position that searching and examining all of the claims including limitations to transgenic plants and animals in the same application presents a serious burden on the Examiner for the reasons given above and in the previous Restriction Requirement.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 28-44 are under consideration.

Priority

4. This application is a continuation of application 09/380,377, filed September 16, 1999, which is a 371 application of PCT/GB98/00468, filed March 2, 1998. Applicant's claim for the benefit of a prior-filed application 09/380,377 under 35 U.S.C. 119(e) and PCT/GB98/00468 under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Acknowledgment is also made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy of UK 9704305.3, filed March 1, 1997, has been filed in parent application 09/380,377, filed September 16, 1999.

Accordingly, the effective priority date of the instant application is granted as March 1, 1997.

Specification

Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

5. The reply filed on December 22, 2004 is not fully responsive to the prior Office Action because of the following omission(s) or matter(s): This application contains sequence disclosures

that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures mailed July 22, 2004.

Specifically the application fails to comply with DCFR 1.821(d), which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The specification discloses nucleotide and amino acid sequences at numerous locations, specifically:

pg 5, lines 7-14,

pg 18, lines 3, 5, 13 and 15,

pg 25, line 28,

pg 27, line 13, and

pg 28, lines 3, 12, 13 and 15.

However, these sequences are not identified by sequence identifiers, nor do the sequence identifiers present in the Sequence Listing filed December 22, 2004 properly annotate the amino acid and nucleotide sequences with those sequences extant within the specification.

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37CFR 1.821(a), must be set forth in the "Sequence Listing". (see MPEP 2422.03).

For the response to this office action to be complete, Applicants are required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino

Acid Sequence Disclosures and provide an amended Specification containing the appropriate SEQ ID NO identifiers.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. **Claims 28-37 and 39-43 are rejected on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 1-3, 5-6, 12-13 and 17-19 of Bulleid et al, U.S. Patent No. 6,171,827 B1. Although the conflicting claims are not identical, they are not

patentably distinct from each other because the method and materials to perform said method claimed in the instant application are encompassed by the patented method(s) and patented materials to perform said patented method(s).

With respect to Claim 28 of the instant application, Applicant claims a method for producing a first pro-collagen in a cell, wherein a nucleic acid sequence encodes a first pro-alpha chain for assembly into said first pro-collagen, wherein said first pro-collagen does not assemble with a second pro-collagen expressed in said cell, and wherein the first pro-collagen comprises a first moiety having activity for assembly into a trimeric pro-collagen C-propeptide, contains a recognition sequence for chain selection, and a second moiety containing a triple helix-forming domain from a pro-alpha chain different from said first type of pro-alpha chain.

Bulleid et al, in claims 12, 13 and 19, recite methods for producing a collagen comprising the production of a pro-collagen polypeptide having a first moiety having activity for assembly into a trimeric pro-collagen C-propeptide and being from a first type of pro-alpha chain, wherein said first moiety contains a recognition sequence for chain selection, and a second moiety containing a triple helix-forming domain from a pro-alpha chain different from said first type of pro-alpha chain. The methods comprise the use of the polypeptide(s) claimed in claims 1-3 and 5-6, the DNA molecule(s) claimed in claim 17, and the expression host cell(s) claimed in claim 18.

Thus, it would be obvious to one of ordinary skill in the art that the method(s) of Bulleid et al are designed to achieve the same results as the method of the instant application, and thus reasonably encompass the instantly claimed invention.

With respect to Claims 29-36 of the instant application, Applicant claims the recognition sequence of the first moiety of the first type of pro-alpha collagen chain to comprise the amino acid sequence shown in SEQ ID NO: 1-8.

Bulleid et al, in claim 3, recite that the recognition sequence of the first moiety of the first type of pro-alpha collagen chain to comprise the amino acid sequence shown in SEQ ID NO: 6-13.

Because both Applicant and Bulleid et al use the generic terms "SEQ ID NO" in their claim language, the Examiner has looked to the specification for definition(s) to better understand the nature of the invention. Upon examination of the respective amino acid sequences of SEQ ID NO: 1-8 of the instant application and SEQ ID NO: 6-13 of Bulleid et al, the following correlations between the instant application SEQ ID NO's and the SEQ ID NO's of Bulleid et al are readily apparent, wherein:

SEQ ID NO:1 is identical to SEQ ID NO:7,

SEQ ID NO:2 is identical to SEQ ID NO:8,

SEQ ID NO:3 is identical to SEQ ID NO:9,

SEQ ID NO:4 is identical to SEQ ID NO:6,

SEQ ID NO:5 is identical to SEQ ID NO:10,

SEQ ID NO:7 is identical to SEQ ID NO:12, and

SEQ ID NO:8 is identical to SEQ ID NO:13.

Thus, it would be obvious to one of ordinary skill in the art that the patented recognition sequences of SEQ ID NO: 6-10 and 12-13 reasonably embrace the instantly claimed recognition sequences of SEQ ID NO: 1-5 and 7-8 recited in Claims 29-33 and 35-36.

SEQ ID NO:6 is identical to SEQ ID NO:11, except for position 10, wherein the Leucine (Leu) of SEQ ID NO:11 is substituted with Isoleucine (Ile) in SEQ ID NO:6. However, the art generally recognizes the substitution of Leucine for Isoleucine to be functionally conservative. Absent evidence to the contrary and a showing of unexpected results, it would be obvious to one of ordinary skill in the art that the patented recognition sequence of SEQ ID NO: 11 anticipates the genus of amino acid sequences identical to SEQ ID NO:11 wherein the amino acid at position 10 may be substituted for another naturally-occurring amino acid, and thus SEQ ID NO:11 reasonably embraces the instantly claimed recognition sequence of SEQ ID NO:6.

With respect to Claim 37 of the instant application, Applicant claims the first and second types of pro-alpha collagen chains to be selected from the group consisting of the pro-alpha 1(I), pro-alpha 2(I), pro-alpha 1(II), pro-alpha 1(III), pro-alpha 1(V), pro-alpha 2(V), pro-alpha 1(XI) and pro-alpha 2(XI).

Bulleid et al, in claims 2 and 6, recite that the first and second moieties from a first type and second type of pro-alpha collagen chain has a recognition sequence selected from the group consisting of the pro-alpha 1(I), pro-alpha 2(I), pro-alpha 1(II), pro-alpha 1(III), pro-alpha 1(V), pro-alpha 2(V), pro-alpha 1(XI) and pro-alpha 2(XI).

Thus, it would be obvious to one of ordinary skill in the art that the patented pro-alpha collagen chains from which the first and second moieties containing a triple helix-forming domain are obtained reasonably embrace the instantly claimed first and second types of pro-alpha collagen chains recited in Claim 37.

With respect to Claims 39-40 of the instant application, Applicant claims a nucleic acid sequence encoding pro-alpha collagen chains to be incorporated into a plasmid, cosmid or phage vector.

Bulleid et al, in claims 17-18, recite a DNA molecule encoding the polypeptide having activity for assembly into a trimeric pro-collagen C-propeptide, wherein the nucleic acid is operably linked to a regulatory sequence that directs expression of said polypeptide. Because Bulleid et al use the generic term "DNA molecule", the Examiner has looked to the specification to better understand the nature of the invention. Bulleid et al disclose that the recombinant DNA in accordance with the invention may be in the form of a vector. The vector may be, for example, a plasmid, cosmid or phage (column 5, lines 47-49).

Thus, it would be obvious to one of ordinary skill in the art that the genus of DNA molecule(s) contemplated by Bulleid et al reasonably embrace the instantly recited vector nucleic acid molecules.

With respect to Claims 41-43 of the instant application, Applicant claims the cell expressing the nucleic acid molecule encoding the pro-collagen molecule to be a eukaryotic cell, e.g. yeast, insect or a mammalian cell.

Bulleid et al, in claim 18, recite a host cell for expressing the DNA molecule encoding the inventive pro-collagen molecule. Because Bulleid et al use the generic term "expression host cell", the Examiner has looked to the specification to better understand the nature of the

invention. Bulleid et al disclose that the expression host cell may be eukaryotic, including yeasts, insects and mammalian cell lines (column 5, lines 64-66).

Thus, it would be obvious to one of ordinary skill in the art that the genus of expression host cells contemplated by Bulleid et al reasonably embrace the instantly recited host cells.

Therefore, claims 1-3, 5-6, 12-13 and 17-19 of U.S. Patent No. 6,171,827 B1 anticipate the Claims 28-37 and 39-43 in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. **Claim 34 is rejected under 35 U.S.C. 112 first paragraph**, because the specification as originally filed does not describe the invention as now claimed. The original disclosure fails to specify the amino acid sequence of SEQ ID NO:6 as now claimed. The amino acid sequence of SEQ ID NO:6 is considered to constitute new matter. This is a new matter rejection.

The elected invention to be examined in this application is drawn to a method for producing a first pro-collagen in an isolated cell, wherein the recognition sequence of the first moiety may comprise the amino acid sequence of SEQ ID NO:6. The amino acid sequence of SEQ ID NO:6 filed December 22, 2004 has not been disclosed in the specification.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN*

RE RASMUSSEN, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure*" (emphasis added).

In the instant case, the specification as originally filed describes that pro-alpha collagen 2(V) comprising the amino acid sequence of GDHQSPNTA*I*.TQMTFLRLL SKE (pg 5, line 12, see also originally filed Claim 8; emphasis added for the Isoleucine (I) residue at position 10). However, the specification is completely silent with respect to the amino acid sequence of SEQ ID NO:6 as now claimed that is identical to said pro-alpha collagen 2(V) comprising the amino acid sequence of GDHQSPNTA*L*.TQMTFLRLL SKE except for the substitution of Leucine (Leu) residue at position 10 (Sequence Listing, pg 3, line 1; emphasis added). Thus, the amendment is a departure from or an addition to the disclosure of the application as filed. Accordingly, it introduces new matter into the disclosure.

For reasons set forth above, the amendment filed December 22, 2004 is objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention. Applicant is required to cancel the new matter in the reply to this Office Action. Alternatively, Applicant is invited to specifically point out where in the specification the support can be found for the amendment made to the disclosure.

8. **Claims 28-44 are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a method of producing a desired pro-collagen polypeptide in a cell, the method comprising:

a) generating a polynucleotide that encodes a pro-alpha collagen chain polypeptide with altered selectivity for pro-alpha chain assembly comprising

i) a first C-terminal propeptide domain from a first pro-alpha chain type having activity for the assembly into a trimeric pro-collagen wherein said propeptide contains the recognition sequence selected from the group consisting of pro-alpha 1(I), pro-alpha 2(I), pro-alpha 1(II), pro-alpha 1(III), pro-alpha 1(V), pro-alpha 2(V), pro-alpha 1(XI) and pro-alpha 2(XI) and having the amino acid sequence selected from the group consisting of SEQ ID NO: 1-8; and,

ii) a second domain containing a triple helix forming domain from a pro-alpha chain type different from said first type,

b) expressing said polynucleotide in a mammalian cell to produce said pro-alpha collagen chain polypeptide, and

c) allowing said polypeptide to assemble into said pro-collagen,

does not reasonably provide enablement for a method of producing a pro-collagen with other specific recognition sequences other than the specifically disclosed amino acid sequences or in cells other than mammalian cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence

of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

With respect to the generation of the inventive collagen molecule(s), the claims are broad for encompassing an enormous genus of pro-collagen molecules obtained from an enormous genus of living organisms. The breadth of the claims encompass the use of any combination of C-terminal domain with any trimeric forming domain for the assembly of the desired pro-collagen. This can result in naturally occurring trimeric formation of molecules which can only be assembled through the use of domain shuffling. Further, the breadth of the claims encompass the assembly of trimeric domains of different species through the use of the C-terminal propeptide domain. When the claims are analyzed in light of the specification, the enormous genus of pro-collagen molecules is expanded even further to encompass pro-collagen derivatives which do not naturally occur and which are created through other molecular manipulations (pg 1, line 2; pgs 3-4, joining ¶; pg 4, lines 7-9) of the known pro-collagen amino acid sequences. For example, a trimeric-forming domain, not necessarily contemplated by Applicant but reasonably encompassed by the claims includes the trimerization domain of Clathrin.

With respect to the host cell expressing the inventive pro-collagen molecule(s), the claims are broad for reasonably encompassing an enormous genus of cell types derived or obtained from an enormous genus of living organisms for the assembly of pro-collagens obtained from an enormous genus of living organisms.

The inventive concept of the instant application is the observation by the Applicant of specific sequences in one C-terminal propeptide, and based on homologous sequences in corresponding pro-collagen molecules, that can be used to direct the nucleation and assembly of

the trimeric forming domains of the pro-collagen molecule while simultaneously avoiding oligomerization between the exogenously provided pro-collagen gene product and endogenously expressed host collagen molecules. Based on previous observations of the assembly of endogenous collagen molecules, a method of domain shuffling is proposed wherein one attaches the C-terminal propeptide of one pro-collagen molecule to the trimeric forming region of another pro-collagen molecule to form a hybrid pro-collagen molecule, wherein the C-terminal propeptide directs nucleation and specific assembly of the hybrid molecules.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The claims encompass the generation any desired collagen molecule and encompass the use of any combination of C-terminal domain with any trimeric forming domain for the assembly of the desired pro-collagen. Further, the breadth of the claims encompass the assembly of trimeric domains of different species through the use of the C-terminal propeptide domain and the use of any type of cell from any species for the assembly of pro-collagens from any species. However, the specification is silent with respect to the creation of other hybrid pro-collagens to demonstrate that the general strategy and the proposed recognition sequences of the other pro-collagen molecules will function as in the single detailed example.

The prior art relevant to the instant invention teaches, for example, experiments that demonstrate the expression of hybrid collagen molecules in insect cells (Myllyharju et al, *of record). Reviewing previous work, Myllyharju el al teach that human pro-collagen can assemble in insect cells but is not stable unless human propyl 4- hydroxylase is also expressed (pg 21824; middle of second column). Further, co-expression of pro-alpha l (1) and pro-alpha 2(I) results in human type I pro-collagen; however, [pro-alpha $2(1)]_3$ do not form (pgs 21824-5; bridging paragraph,). Walmsley et al (*of record) also teach the importance of propyl 4- hydroxylase in the stability and secretion of pro-collagen molecules (pg 14884; summarized in abstract, pg 14886; figure 1). Walmsley et al teach that derivatives of collagen molecules, in this case mini-genes absent of triplex forming regions, can be created and expressed, however the polypeptides encoded by these mini-genes will not assemble in pro-collagen molecules (pg 14891; top of column 2). Therefore, by extension, not all possible derivatives of pro-collagen can be used to

direct the formation of a desired collagen molecule. Applicant has proposed a potential method for the assembly of pro-collagen molecules; however, because the assembly of collagen is a complex multi-step process, modifications to the endogenous gene may result in modifications which would produce a hybrid molecule incapable of producing tile desired collagen.

As taught in the specification, the proposed mechanism for nucleation and assembly of pro-collagen chains can be found in the C-terminal propeptide portion of the pro-collagen chain (pgs 27-28; bridging paragraph). However, the art teaches that when intact genes for pro-collagen are expressed in non-native host cells, in this case chicken pro-collagen in mouse NIH3T3 cells, no self-association was observed for either pro-alpha 1 (V1) or pro-alpha 2(V1) (Colombatti et al, pg 785; summarized in abstract, *of record) suggesting that not all combinations of pro-collagen chains will undergo the proper processing and/or assembly in any type of cell. Furthermore, because of the lack of homology of pro-collagen chains between species, the pro-alpha 1(VI) or pro-alpha 2(VI) from chicken do not form the chimeric chicken/mouse heteromers one expects based on known structures and homology, suggesting further that domain switching between pro-collagen chains will not result in the formation of any and all combinations of desired pro-collagen chains (pg 785; summarized in abstract). Thus, the art recognizes considerable uncertainty regarding the normal biological function and assembly of intact pro-collagen chains, including the effect of domain swapping of pro-collagen genes, in unique host cells that cannot be predicted simply by homology or known structure.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification gives specific guidance on how the specific amino acids in the C-terminal domain result in the recited recognition sequence of Claim 32 (pg 25, Section 2.3) and using sequence comparison programs, defines the amino acid of the recognition sequences of other known collagen molecules. The specification teaches specifically how one C-terminal domain can be used to assemble the trimeric domain of another pro-collagen molecule. The art of record and the present specification teach that these molecules can self assemble into trimeric collagen molecules. The specification proposes a potential method for the assembly of pro-collagen molecules, however, because tile assembly of collagen is a complex multi-step process,

modifications to the endogenous gene may result in modifications which would produce a hybrid molecule incapable of producing the desired collagen.

Therefore, the central issue is whether the present specification provides the necessary guidance to provide a nexus between the art recognized limitations of producing all possible combinations of pro-collagen chains contemplated by Applicant that will undergo the proper processing and/or assembly in any type of cell encompassed by the claimed host cells. In particular, read in light of the specification, one embodiment is the production of heteromeric collagen chains between recombinant pro-collagen polypeptide species which has presently not been demonstrated in art.

However, the specification does not disclose any specific detail of expressing the pro-collagen chain in an isolated cell. It is noted that the working examples teach the synthesis of the recombinant pro-collagen polypeptides in the context of the rabbit reticulolysate expression system and semi-permeabilized human sarcoma cells (Examples 4-12). The art recognizes that this artificial *in vitro* expression system does not adequately represent expression and synthesis of an artisan's polypeptide within the enormous genus of physically intact host cells grown under diverse environmental conditions that take into consideration important variables such as the types of growth media, the concentration of metabolic gasses, the proliferative state, the cell density, etc... as each cell type has its own specific growth and environmental requirements and biochemical capabilities to synthesize the desired polypeptide. Furthermore, with respect to plant cells, Ruggiero et al (* of record) demonstrate that although one can express the pro-alpha 1(I) chain in plants, it is not clear that expression of other pro-collagen chains, and in particular the hybrid genes recited in the claims, will be expressed, processed and assembled properly in all possible plant host cells encompassed by the enormous genus of eukaryotic host cells.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Applicants have described a potential method for the assembly of desired collagen molecules and prophetic recognition sequences based on computer homology searches; however, for the reasons detailed above, without the reduction to practice of more than one example, it is not clear if the predicted methodology will be operative for all the different combinations of collagen molecules encompassed in the scope of the claims. Further, Applicants have not

addressed the problem of the extensive post-translational modification of collagen molecules and the need of other enzymes, such as the propyl 4- hydroxylase in yeast, to obtain a collagen molecule which would assemble properly, and so have not provided the proper guidance to achieve the proposed method in all types of cells.

With respect to the genus of alterations resulting in a collagen polypeptide having the stability and/or biological activity for assembling into a trimeric pro-collagen C-propeptide, the Examiner notes that the art of record teaches that not all embodiments are enabled by the instant disclosure. While methods of isolating or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen - by a trial and error process - for all polypeptide variants having a substantial number of modifications as encompassed by the claims for those polypeptides having the desired activity/utility. The reference of Guo et al. (Proc Natl Acad Sci 101(25):9205-9210, 2004) teaches a study suggesting that the percentage of variants having multiple substitutions that maintain activity appears to be exponentially related by the simple formula: $(.66)^x$ X 100% (where x is the number of mutations introduced). The specification discloses a 23 amino acid recognition sequence motif involved in the specificity of association between C-terminal propeptide domains of pro-alpha chains during the formation of pro-collagens (pg 5, lines 1-15). Within the 23 amino acid motif of SEQ ID NO:4, only five residues are strictly conserved (Figure 2). Thus, up to 18 amino acids within this motif can be simultaneously mutated. According to Guo et al., only $(.66)^{18}$ X 100%, or 0.1%, of random mutants of SEQ ID NO:4, for example, would be active. Applicant further contemplates the use of cognate recognition site sequences provided in SEQ ID NO: 1-3 and 5-8, and derivatives thereof. Thus, a significant number of variants for each recognition sequence must be screened in order to isolate those variants having the desired collagen oligomerization activity. The art clearly does not typically engage in the screening of such a large number of variants to isolate those relatively few variants that would have the desired activity/utility. That screening this number of variants is not routinely practiced in the art is evidenced by Hult and Berglund (Curr Opin Biotechnol 14:395-400, 2003), which teaches that recent attempts to randomly obtain variants of a given polypeptide included screening of "6000 transformants" (p. 396, left column, top) or 3.4×10^7 variants (p. 396, left column, bottom). In view of the number of non-enabled embodiments of the inventive pro-collagen genes contemplated to be expressed in the enormous

genus of isolated cells, it would constitute undue experimentation to one of ordinary skill in the art to generate the enormous genus of pro-collagen genes to fulfill the limitations of the instant claims.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a method of producing a desired pro-collagen polypeptide in a cell, the method comprising:

a) generating a polynucleotide that encodes a pro-alpha collagen chain polypeptide with altered selectivity for pro-alpha chain assembly comprising

i) a first C-terminal propeptide domain from a first pro-alpha chain type having activity for the assembly into a trimeric pro-collagen wherein said propeptide contains the recognition sequence selected from the group consisting of pro-alpha 1(I), pro-alpha 2(I), pro-alpha 1(II), pro-alpha 1(III), pro-alpha 1(V), pro-alpha 2(V), pro-alpha 1(XI) and pro-alpha 2(XI) and having the amino acid sequence selected from the group consisting of SEQ ID NO: 1-8; and,

ii) a second domain containing a triple helix forming domain from a pro-alpha chain type different from said first type,

b) expressing said polynucleotide in a mammalian cell to produce said pro-alpha collagen chain polypeptide, and

c) allowing said polypeptide to assemble into said pro-collagen, is proper.

9. **Claims 28-44 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically:

Claim 28 is vague and unclear in the recitation of 'said pro-alpha chain for assembly into said first pro-collagen with other pro-alpha chains having said activity' because at least two types of pro-alpha chains are recited in the embodiments set forth in (i) and (ii). Further, the recitation said activity lacks antecedent basis to pro-alpha chains since the only previous reference is to an

activity of a 'first moiety' in (i). Clearly setting forth the nature of the activity each of the molecules possesses or more clearly setting forth limitations for assembly would obviate the basis of the rejection.

Claim 37 recites the limitation 'said second type of pro-alpha chain' in reference to Claim 28. There is insufficient antecedent basis for this limitation in the claim. Claim 28, part (ii), recites 'a second moiety containing a triple helix-forming domain from a pro-alpha chain different from said first type', but also recites a second pro-collagen that does not assemble with a first pro-collagen.

Dependent claims are included in the basis of the rejection because although they recite and encompass specific domains, they do not clarify the nature of any activity or how the activity is related from one domain to another.

Correction and clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

10. **Claims 28-32, 37 and 39-43 are rejected under 35 U.S.C. 102(b) and 35 U.S.C. 102(e)** as being anticipated by Prockop et al (U.S. Patent No. 5,593,859, January 14, 1997).

The claims are drawn to a method of producing a desired pro-collagen by creating recombinant pro-alpha collagen polypeptides wherein the pro-alpha collagen polypeptide comprises a C-terminal propeptide containing the recognition sequence of a first type of pro-collagen (specifically SEQ ID NO: 1-8) and another portion comprising a triple helix-forming domain of a second type of pro-collagen that is different than the first type of collagen polypeptide, wherein said desired recombinant pro-collagen polypeptide does not assemble with an endogenously-expressed pro-collagen molecule and is encoded by a gene in an isolated cell, wherein the isolated cell is a yeast, insect or mammalian cell.

With respect to Claim 28, Prockop et al teach a method of expression one or more pro-collagen genes, wherein the genes may be mutant, variant, hybrid or recombinant (column 5, lines 1-17). The modified gene would be made up of a number of discrete regions (column 5, line 24). Prockop et al. teach hybrid pro-collagen genes which encode hybrid polypeptides (column 2; lines 25-57), specifically, the 5' COL1A1 encoding a portion of the pro-alpha l type I chain is linked to the COL2AI gene which encodes the pro-alpha 1 type III chain (Table 1).

With respect to Claims 29-32 and 37, Prockop et al disclose the contemplation of alpha 1(I), alpha 1(II), alpha 1(III) and alpha 2(I) collagen genes, or specifically engineered forms therof, for use in the invention (column 5, lines 35-37; column 6, lines 56-67).

With respect to Claims 39-40, Prockop et al teach that the nucleic acid encoding the inventive pro-collagen polypeptide may be expressed in a large number of expression vectors commonly known in the art, as optimized by the desired cell type to express said polypeptide. For example, Prockop et al demonstrate expression of pro-collagen from a cosmid plasmid vector (Example 3, column 8, line 56), baculoviral vectors (Example 7, column 11, lines 6-20) and yeast expression vectors (Example 8, column 12, lines 57-60). Prockop et al specifically teach that one can express multiple copies of the gene and that one can engineer sites to produce "desired regions of pro-collagen or collagen" (column 10; lines 52-56).

With respect to Claims 41-43, Prockop et al provide the guidance and teach the necessary steps for a method in which the recombinant pro-collagen polynucleotides can be expressed in yeast (columns 12-14; Examples 8-9), insect cells (columns 10-12; Example 7) and mammalian cells (column 7-10; Examples 1-6) to produce the desired pro-alpha collagen chains and/or assembled pro-collagen in these cells.

Thus, Prockop et al anticipate Claims 28-32, 37 and 39-43.

11. **Claims 28-33 and 35-43 are rejected under 35 U.S.C. 102(e)** as being anticipated by Bulleid et al (U.S. Patent No. 6,171,827 B1).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

With respect to Claim 28, Bulleid et al teach the production of novel collagens in which combinations of alpha chains which are not seen in nature because of the assembly-directing effect of the natural C-propeptides (column 4, lines 49-56). The invention allows the protein engineer to construct novel collagens having a non-natural combination of alpha chains (columns 3-5). The inventive pro-collagen molecules may be expressed from a recombinant DNA system and transformed/transfected into a host expression cell (column 5, lines 40-66).

With respect to Claims 29-33 and 35-36, Bulleid et al teach the recognition sequences having the amino acid sequences of SEQ ID NO: 6-13 (column 8, lines 24-27), wherein SEQ ID NO:1 is identical to SEQ ID NO:7, SEQ ID NO:2 is identical to SEQ ID NO:8, SEQ ID NO:3 is identical to SEQ ID NO:9, SEQ ID NO:4 is identical to SEQ ID NO:6, SEQ ID NO:5 is identical to SEQ ID NO:10, SEQ ID NO:7 is identical to SEQ ID NO:12, and SEQ ID NO:8 is identical to SEQ ID NO:13.

With respect to Claims 37-38, Bulleid et al teach that the recognition site sequence may be, or substituted for, a recognition sequence selected from the group consisting of the pro-alpha 1(I), pro-alpha 2(I), pro-alpha 1(II), pro-alpha 1(III), pro-alpha 1(V), pro-alpha 2(V), pro-alpha 1(XI) and pro-alpha 2(XI) (column 3, lines 50-52; column 4, lines 7-8). Similarly, the second moiety may comprise at least a collagen alpha chain selected from the same group (column 4, lines 60-65).

With respect to Claims 39-40, Bulleid et al disclose that the recombinant DNA in accordance with the invention may be in the form of a vector. The vector may be, for example, a plasmid, cosmid or phage (column 5, lines 47-49).

With respect to Claims 41-43, Bulleid et al teach the expression host cell may be eukaryotic, including yeasts, insects and mammalian cell lines (column 5, lines 64-66).

Thus, Bulleid et al anticipate Claims 28-33 and 35-43.

12. **Claims 28-33 and 35-43 are rejected under 35 U.S.C. 102(f)** because the applicant did not invent the claimed subject matter. The prior art reference (U.S. Patent No. 6,171,827 B1) establishes that two individuals, Neil Bulleid and Karl Kadler, are the inventors of the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. **Claims 28-44 are rejected under 35 U.S.C. 103(a)** as being obvious over Bulleid et al (U.S. Patent No. 6,171,827 B1), as evidenced by Barr et al (U.S. Patent No. 5,460,950).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of

invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Bulleid et al teach the production of novel collagens in which combinations of alpha chains which are not seen in nature because of the assembly-directing effect of the natural C-propeptides (column 4, lines 49-56). The recognition sequences necessary and sufficient to determine the type-specific assembly of the moieties to which it is attached may be a recognition sequence selected from the group consisting of the pro-alpha 1(I), pro-alpha 2(I), pro-alpha 1(II), pro-alpha 1(III), pro-alpha 1(V), pro-alpha 2(V), pro-alpha 1(XI) and pro-alpha 2(XI) (column 3, lines 50-52; column 4, lines 7-8) and have the amino acid sequences of SEQ ID NO: 6-13 (column 8, lines 24-27), wherein SEQ ID NO:1 is identical to SEQ ID NO:7, SEQ ID NO:2 is identical to SEQ ID NO:8, SEQ ID NO:3 is identical to SEQ ID NO:9, SEQ ID NO:4 is identical to SEQ ID NO:6, SEQ ID NO:5 is identical to SEQ ID NO:10, SEQ ID NO:7 is identical to SEQ ID NO:12, and SEQ ID NO:8 is identical to SEQ ID NO:13.

The invention allows the protein engineer to construct novel collagens having a non-natural combination of alpha chains (columns 3-5). The inventive pro-collagen molecules may be expressed from a recombinant DNA system and transformed/transfected into a host expression cell (column 5, lines 40-66), wherein such host cells may be eukaryotic cells, including yeasts, insects and mammalian cell lines.

Bulleid et al do not teach the use of BHK, 3T3, CHO and COS cells, as recited in Claim 44. However, at the time of filing of the instant application, the art recognized that these mammalian cell lines were generally useful for the expression of exogenous proteins (Barr et al, column 14, lines 7-35).

Bulleid et al also do not teach SEQ ID NO:6. However, SEQ ID NO:6 is identical to SEQ ID NO:11, except for position 10, wherein the Leucine (Leu) of SEQ ID NO:11 is substituted with Isoleucine (Ile) in SEQ ID NO:6.

It would have been obvious to one of ordinary skill in the art to modify the method of Bulleid et al with the method of the instant application with a reasonable chance of success because Bulleid et al disclose how an artisan may express and synthesize recombinant pro-collagen molecules that do not oligomerize with any pro-collagen molecules endogenously expressed in the given host cell. An artisan would be motivated to modify the method of Bulleid et al because the prior art teaches that the method(s) is useful for the synthesis and recovery of novel, non-naturally-occurring collagen molecules.

Absent evidence to the contrary and a showing of unexpected results, it also would have been obvious to one of ordinary skill in the art to modify the Leucine residue at position 10 of the recognition sequence of SEQ ID NO:11 with an Isoleucine with a reasonable chance of success because the art generally recognizes the substitution of Leucine for Isoleucine to be functionally conservative. Applicant discloses the prototypical C-propeptide motif which directs chain assembly (pg 25, Section 2.3), wherein the most divergent residues are underscored. It is noted that the Leucine/Isoleucine residue at issue is encompassed within this most divergent motif. An artisan would be motivated to substitute amino acids of SEQ ID NO:11 because some amino acids in the recognition sequence are less well conserved than others but may form a core-recognition sequence that is of critical importance in the selection process, and thus modification of any given amino acid will be advantageous in the optimization of the inventive recognition site so as to promote trimerization with a desired pro-collagen molecule and inability to trimerize with a non-desired pro-collagen molecule simultaneously expressed in the given host cell.

Thus, Claims 28-44 are *prima facie* obvious.

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036.

The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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